APPENDIX B

NATIONAL ACADEMY OF SCIENCES-NATIONAL RESEARCH COUNCIL
Division of Medical Sciences

USES OF THE ROSTER OF VETERAN TWINS

Seymour Jablon

During the last 10 years, with the support of the Veterans Administration (VA), the Department of Defense (DOD), and the National Institutes of Health, the Follow-Up Agency of the Division has compiled a list of pairs of male twins both of whom served in the armed forces during World War II; hence the name, "Veteran Twins". Veterans were chosen because, from the files of the VA and the DOD, a very large amount of medical and other information is available for veterans. This information includes the fact of survival or mortality (including cause of death), any physical defects present at entry into military service, all diagnoses assigned during hospitalizations while in military service or in VA hospitals afterwards, and so on. In fact, the whole program of the Follow-Up Agency is based on the exploitation for medical research purposes of these files, which are maintained for administrative reasons. So the roster of veteran twins is no different in this respect from the remainder of the program.

The difficult part of the job of making the roster was to find out which veterans were twins. Neither the VA nor the military keeps tract of the fact of twins in any regular way. Therefore, the individual state birth records had to be searched for multiple male births, and the names checked against military and VA files. More than 100,000 names were checked, and 47,000 were matched. However, we were interested only in pairs of whom both were veterans; there were 32,000 of these. That is, we have 16,000 pairs of white, male twins, all veterans, born in the years 1917 to 1927. After identifying these 32,000 men, our next job was to obtain medical histories and to determine which pairs were monozygotic (identical) and which dizygotic (fraternal). We now have in hand all information on mortality through 1964, all military and VA hospitalizations, and, from about 18,000 of the men at this time, questionnaires giving medical histories. With respect to diagnosing zygosity, we have experimented with a variety of techniques. We obtained fingerprint records from the FBI for about one-third of the men, and these have proved to be quite useful, although not as useful as we had hoped at first. Unfortunately, it has not been possible to get the FBI to search its files for the missing two-thirds. However, Cederlöf and Friberg of the Karolinska Institute in Stockholm had reported that they had found in the Swedish Twin Registry a rather simple solution to the problem of obtaining zygosity diagnoses in a large, nationwide group of like-sexed twins: You ask them! So we tried asking them, and it turned out that the twin's opinions were 96 percent accurate. We checked their opinions on a sample of about 250 pairs. The serologic diagnoses were made by the Department of Human Genetics of the University of Michigan, under Dr. James Neel. We find that about 44 percent of the pairs are identical, and 56 percent are fraternal.

The use of twins goes back about 90 years to Francis Galton, who was concerned with the problem of the relative importance of what he called "Nature and nurture." We are concerned with the same problems today, except that now we generally call it "heredity and environment." Also, today we are acutely aware that many problems in the area of health, heredity and environment are so closely intertwined that one cannot speak accurately of the relative importance of each.

Following Galton, a large number of investigators used twins to study genetic factors in the etiology of certain diseases - malformations and the like. Usually the series were small, and were collected haphazardly, as pairs somehow came to the attention of the investigator. For a variety of reasons, there have been few twin panels really suitable for the study of genetic factors in chronic disease, such as malignancy or cardiovascular disease. One of our great hopes for the roster of veteran twins is that we may be able to bring some solid evidence to what have been largely speculative discussions of such questions as: Is coronary artery disease all a question of nutrition or exercise or some combination of environmental factors, or are there also important genetic factors?

To use twins in assessing the importance or relevance of genetic factors in causing a disease, one traditionally classifies all the pairs as concordant for the disease (both either have the disease or do not have it) or as discordant. One also classifies the twins as monozygotic or dizygotic. Monozygotic twins have identical genes, and dizygotic twins share an average of only 50 percent of their genes. If for some disease one finds that all monozygotic twins are concordant, but not all dizygotic twins, it is easy to see that there is a strong argument that the genes are somehow intimately concerned in the etiology of the disease.

Unfortunately, things are seldom so simple. Except for a few conditions, like color blindness, that are under exclusively genetic control, in neither kind of twins will all pairs be concordant. One is then reduced to comparing the concordance rates in the two kinds of twins, and there is a formula that purports to measure the "heritability" of a condition in terms of the concordance rates. However, this formula itself suffers from a disease--an almost fatal disease. It depends on an assumption that is contrary to fact: that identical and fraternal twins share their environments to the same extent. It is tempting to assume that the only difference between monozygotic and dizygotic twins is the difference in the proportion of shared genes; but a number of studies, including the Swedish twin studies, have shown that identical twins more often choose the same friends, follow the same kind of work, smoke or do not, etc. Therefore, one is faced with the possibility that it may be the more similar environment, rather than the identical genes, that explains the higher concordance rate in identical twins.

I don't have to point out that this problem is not really peculiar to twin studies. It is merely one additional manifestation of a general problem that affects all epidemiologic studies of humans: that they are observational, rather than experimental. We do not randomize people to diets or to occupations, but take our study materials as they come and take account of biases

as well as we can. In this case, we have to consider occupational histories or whatever else may seem appropriate in interpreting results.

Beyond the kinds of studies measuring concordance, there is great interest in the use of identical twins in the study of environmental factors in relation to disease. For example, suppose that one had a large number of identical pairs in which one twin was a nonsmoker and the other smoked cigarettes. Study of these twins could lead to an evaluation of the role of smoking in causing various diseases, eliminating possible genetic influences. Some persons have advanced the hypothesis that the observed association between, say, cigarette smoking and lung cancer may occur because some common genetic factor leads to both. In fact, we are hopeful that we may be able to attack this problem through the veteran twin roster.

We have been developing the roster as a resource. Although obviously there are many things that the staff wishes to do with this material, we hope that it will find its greatest usefulness as a resource in the hands of outside investigators who have significant problems that can be worked out by observations on these twins. We on the staff would expect to work in collaboration with such outside investigators. There is a specific problem of protecting the twins from over-solicitation, and the staff from over-work!--and requests for access to the panel will be monitored by the Division's Committee on Epidemiology and Veterans Follow-Up Studies. We have just declared the panel ready--in fact, the paper in which the announcement is made is still in press--and we already have four requests to take to our Committee in April.